CYCLIC PEPTIDE ANTIFUNGAL AGENTS

FIELD OF THE INVENTION

The present invention relates to anti-fungal/anti-parasitic agents, in particular, derivatives of Echinocandin compounds and their use in the treatment of fungal and parasitic infections.

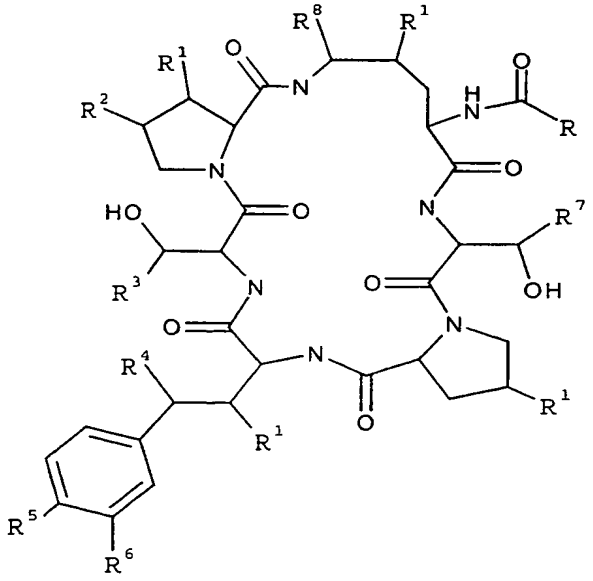
BACKGROUND ART

A number of naturally occurring cyclic peptides are known in the art including echinocandin B (A30912A), aculeacin, mulundocandin, sporiofungin, L-671,329, and S31794/F1. In general, these cyclic peptides can be structurally characterized as a cyclic hexapeptide core (or nucleus) with an acylated amino group on one of the core amino acids. This acyl group is typically a fatty acid moiety forming a side chain off the nucleus. For example, echinocandin B has a linoleoyl side chain while aculeacin has a palmitoyl side chain.

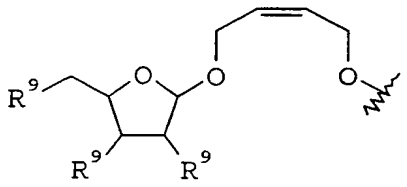
These natural products have limited inherent antifungal and antiparasitic properties. The natural compounds can be structurally modified in order to enhance these properties or improve the compound's stability and/or water solubility. Turner et al. *Cur. Pharm. Des.* 2:209 (1996). For example, the fatty acid side chain can be removed from the cyclic peptide core to yield an amino nucleus which can be re-acylated to yield semi-synthetic compounds.

DISCLOSURE OF THE INVENTION

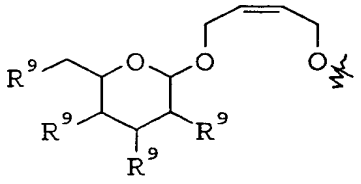
A compound represented by structure I is provided



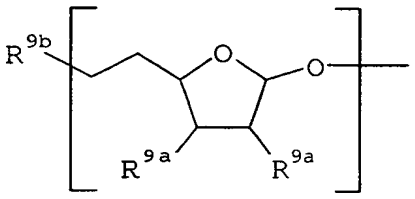
where R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R^1 is independently -H, -OH or -O-Pg; R^2 is -H, $-CH_3$, $-NH_2$, or -NH-Pg; R^3 is -H, $-CH_3$, $-CH_2CONH_2$, $-CH_2CONH$-Pg, $-CH_2CH_2NH_2$, or $-CH_2CH_2NH$-Pg; R^5 is -OH, $-OSO_3H$, or $-OPO_2HR^a$, where R^a is hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, phenoxy, *p*-halophenyl, *p*-halophenoxy, *p*-nitrophenyl, *p*-nitrophenoxy, benzyl, benzyloxy, *p*-halobenzyl, *p*-halobenzyloxy, *p*-nitrobenzyl, or *p*-nitrobenzyloxy; R^6 is -H, -OH, or $-OSO_3H$; R^7 is -H or $-CH_3$; R^4 and R^8 are independently, hydrogen, or hydroxy and at least one of R^4 and R^8 is a sugar moiety of the formula



or



where R^9 is independently -H, -OH, $-N_3$, -O-Pg, $-NH_2$, -NH-Pg, $-OPO_2R^a$, or a second sugar moiety containing one to three sugar units of



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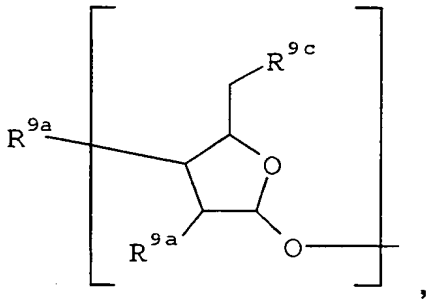

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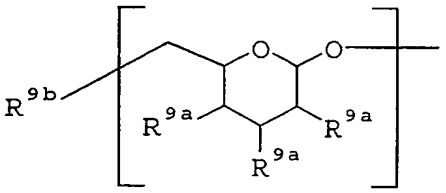

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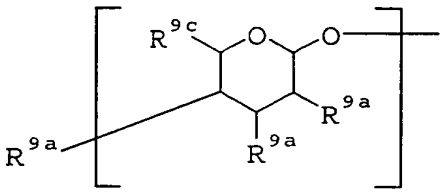


, and mixtures thereof, where R^{9a} is -H, -OH, $-N_3$, $-NH_2$, -O-Pg, or -NH-Pg, R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg, R^{9c} is $-CH_3$, $-CH_2OH$, $-CH_2N_3$, $-CH_2OSO_3H$, $-CH_2NH$-Pg, $-CH_2O$-Pg, $-CO_2H$, or $-CO_2$-Pg, where R^a is as defined above, and no more than one R^9 is represented by said second sugar moiety; Pg is a protecting group (i.e., -O-Pg is a hydroxy protecting group, -NH-Pg is an amino protecting group, $-CH_2CONH$-Pg is an

amido protecting group and -CO_2-Pg is a carboxy protecting group); and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

The invention encompasses a pharmaceutical formulation is containing one or more pharmaceutical carriers, diluents or excipients and a Compound I described above.

The invention encompasses a method for inhibiting fungal and parasitic activity by administering an effective amount of Compound I to a recipient in need thereof.

"Alkyl" is a hydrocarbon radical of the general formula C_nH_{2n+1} containing from 1 to 30 carbon atoms unless otherwise indicated. The alkane radical can be straight, branched, cyclic, or multi-cyclic. The alkane radical can be substituted or unsubstituted. The alkyl portion of an alkoxy group, alkylthio group or alkanoate have the same definition as above.

"C_1-C_{12} alkyl" is a straight or branched saturated alkyl chain of from one to twelve carbon atoms. C_1-C_{12} alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, 5-methylpentyl, hexyl, heptyl, 3,3-dimethylheptyl, octyl, 2-methyl-octyl, nonyl, decyl, undecyl and dodecyl. "C_1-C_{12} alkyl" includes "C_1-C_6 alkyl", "C_1-C_4 alkyl", and "C_3-C_{12} cycloalkyl".

"C_3-C_{12} cycloalkyl" is a cyclic saturated alkyl chain of from 3 to 12 carbon atoms. Moreover, the term "C_3-C_{12} cycloalkyl" includes "C_3-C_7 cycloalkyl", *i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. "C_1-C_{12} alkoxy" refers to a C_1-C_{12} alkyl group attached through an oxygen atom. C_1-C_{12} alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, sec-butoxy, n-pentoxy, 5-methyl-hexoxy, heptoxy, octyloxy, decyloxy and dodecyloxy. "C_1-C_{12} alkoxy" includes "C_1-C_6 alkoxy", "C_3-C_7 alkoxy", and "C_1-C_4 alkoxy".

"C_1-C_{12} alkylthio" is a C_1-C_{12} alkyl group attached through a sulfur atom. C_1-C_{12} alkylthio groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, 3-methyl-heptylthio, octylthio and 5,5-dimethyl-hexylthio. "C_1-C_{12} alkylthio" includes "C_1-C_6 alkylthio" and "C_1-C_4 alkylthio."

"Alkenyl" is an acyclic hydrocarbon containing at least one carbon-carbon double bond. The alkene radical can be straight, branched, cyclic, or multi-cyclic, substituted or unsubstituted.

"Alkynyl" is an acyclic hydrocarbon containing at least one carbon-carbon triple bond. The alkyne radical can be straight, or branched, substituted or unsubstituted.

"C_2-C_{12} alkynyl" is a straight or branched mono-alkynyl chain having from two to twelve carbon atoms. C_2-C_{12} alkynyl groups include, but are not limited to, ethynyl, 1-propyn-1-yl, 1-propyn-2-yl, 1-butyn-1-yl, 1-butyn-3-yl, 1-pentyn-3-yl, 4-pentyn-2-yl, 1-

hexyn-3-yl, 3-hexyn-1-yl, 5-methyl-3-hexyn-1-yl, 5-octyn-1-yl, 7-octyn-1-yl and 4-decyn-1-yl, 6-decyn-1-yl.

"Aryl" is aromatic moieties having single (e.g., phenyl) or fused ring systems (e.g., naphthalene, anthracene, phenanthrene, etc.). The aryl groups can be substituted or unsubstituted. Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.).

"Heteroaryl" is an aromatic moiety containing at least one heteratom within the aromatic ring system (e.g., pyrrole, pyridine, indole, thiophene, furan, benzofuran, imidazole, pyrimidine, purine, benzimidazole, quinoline, etc.). The aromatic moiety can consist of a single or fused ring system. The heteroaryl groups can be substituted or unsubstituted.

Within the field of organic chemistry and particularly within the field of organic biochemistry, it is widely understood that significant substitution of compounds is tolerated or even useful. Alkyl group allows for substituents which is a classic alkyl, such as methyl, ethyl, propyl, *n*-butyl, *i*-butyl, *t*-butyl, hexyl, isooctyl, dodecyl, stearyl, etc. The term group includes substitutions on alkyls which are common in the art, such as hydroxy, halogen, alkoxy, carbonyl, keto, ester, carbamato, etc., as well as including the unsubstituted alkyl moiety. The substituents should not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. The same is true for each of the other groups (i.e., aryl, alkynyl, alkenyl, heteroaryl). Suitable substituents for any of the groups defined above include alkyl, alkenyl, alkynyl, aryl, halo, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, mono- and di-alkyl amino, quaternary ammonium salts, aminoalkoxy, hydroxyalkylamino, aminoalkylthio, carbamyl, carbonyl, carboxy, glycolyl, glycyl, hydrazino, guanyl, and combinations thereof.

"Halo" refers to chloro, fluoro, bromo and iodo.

"O-Pg" and "hydroxy protecting group" refer to a substituent of a hydroxy group commonly employed to block or protect the hydroxy functionality while reactions are carried out on other functional groups on the compound. This substituent, when taken with the oxygen to which it is attached, can form an ether, *e.g.*, methyl, methoxymethyl, and benzyloxymethyl ether, a silyl ether, an ester, *e.g.* acetoxy, or a sulfonate moiety, *e.g.* methane and p-toluenesulfonate. The exact genus and species of hydroxy protecting group is not critical so long as the derivatized hydroxy group is stable to the conditions of subsequent reaction(s) and the protecting group can be removed at the appropriate point without disrupting the remainder of the molecule. A preferred hydroxy protecting group is acetyl. Specific examples of hydroxy protecting groups are described in Greene,

"Protective Groups in Organic Synthesis," John Wiley and Sons, New York, N.Y., (2nd ed., 1991), (*Greene*) chapters 2 and 3 and Preparations and Examples sections herein.

"NH_p-Pg" and "amino protecting group" are a substituent of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. When p is 0, the amino protecting group, when taken with the nitrogen to which it is attached, forms a cyclic imide, *e.g.*, phthalimido and tetrachlorophthalimido. When p is 1, the protecting group, when taken with the nitrogen to which it is attached, can form a carbamate, *e.g.*, methyl, ethyl, and 9-fluorenylmethylcarbamate; or an amide, *e.g.*, N-formyl and N-acetylamide. The exact genus and species of amino protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and the protecting group can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino protecting group(s). Preferred amino protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl, phthalimido, and benzyloxycarbonyl (CbZ). See, *Greene* at chapter 7.

"-CO_2-Pg" and "carboxy protecting group" are a substituent of a carbonyl commonly employed to block or protect the carboxy functionality while reactions are carried out on other functional groups on the compound. This substituent, when taken with the carbonyl to which it is attached, can form an ester, *e.g.*, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, benzyl, substituted benzyl, benzhydryl, substituted benzhydryl, trityl, substituted trityl, and trialkylsilyl ester. The exact species of carboxy protecting group is not critical so long as the derivatized carboxy group is stable to the conditions of subsequent reaction(s) and the protecting group can be removed at the appropriate point without disrupting the remainder of the molecule. Other examples of groups referred to by the above terms are described in *Greene*, at chapter 5.

"C(O)NH-Pg" and "amido protecting group" are a substituent of an amide commonly employed to block or protect the amino portion while reacting other functional groups on the compound. This protecting group, when taken with the nitrogen to which it is attached, can form an amide, *e.g.* N-allyl, N-methoxymethyl, and N-benzyloxymethyl amide. The exact species of amido protecting group employed is not critical so long as the derivatized amido group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and the protecting group can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amido protecting group(s). Other examples of groups referred to by the above terms are described in *Greene*, chapter 7, pg. 397.

"Carbonyl activating group" is a substituent of a carbonyl that promotes nucleophilic addition reactions at that carbonyl. Suitable activating substituents have a net electron withdrawing effect on the carbonyl. Such groups include, but are not limited to, alkoxy, aryloxy, nitrogen containing aromatic heterocycles, or amino groups such as oxybenzotriazole, imidazolyl, nitrophenoxy, pentachlorophenoxy, N-oxysuccinimide, N,N'-dicyclohexylisoure-O-yl, N-hydroxy-N-methoxyamino; acetates, formates, sulfonates such as methanesulfonate, ethanesulfonate, benzenesulfonate, or p-tolylsulfonate; and halides such as chloride, bromide, or iodide.

"Pharmaceutical" or "pharmaceutically acceptable" are substances substantially non-toxic and substantially non-deleterious to the recipient. "Pharmaceutical formulations" are those in which the carrier, solvent, excipients and salt are compatible with the active ingredient of the formulation (i.e., Compound I).

"Pharmaceutical salt" or "pharmaceutically acceptable salt" are salts of the compounds represented by structure I that are substantially non-toxic to the recipient at the doses administered. Typical pharmaceutical salts include those prepared by reaction of the compounds of the present invention with a mineral or organic acid or inorganic base. Such salts are known as acid addition and base addition salts. For further exemplification of pharmaceutical salts, see *e.g.* Berge et al., *J. Pharm. Sci.*, 66:1 (1977).

"Solvate" represents an aggregate that comprises one or more molecules of the solute, such as a formula I compound, with one or more molecules of a pharmaceutical solvent, such as water, ethanol, and the like. "Suitable solvent" is any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

"Thermodynamic base" is a base which provides a reversible deprotonation of an acidic substrate or is a proton trap for those protons that can be produced as byproducts of a given reaction, and is reactive enough to effect the desired reaction without significantly effecting any undesired reactions. Examples of thermodynamic bases include, but are not limited to, acetates, acetate dihydrates, carbonates, bicarbonates, C_1-C_4 alkoxides, and hydroxides (*e.g.* silver, lithium, sodium, or potassium acetate, acetate dihydrate, carbonate, bicarbonate, methoxide, or hydroxide), tri-(C_1-C_4 alkyl)amines, or aromatic nitrogen containing heterocycles (*e.g.* imidazole and pyridine).

"Inhibiting" includes prohibiting, stopping, retarding, alleviating, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of the growth or any attending characteristics, symptoms, and results from the existence of a parasite or fungus. These methods include both medical therapeutic (acute) and/or prophylactic (prevention) administration as appropriate.

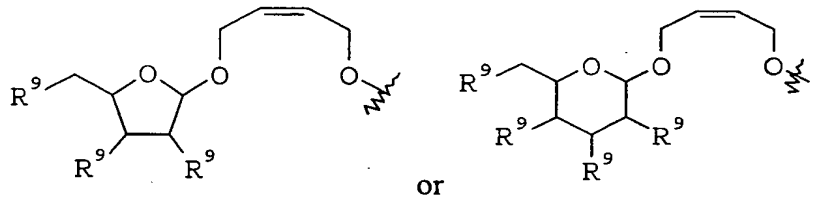
"Effective amount" refers to an amount of a compound of formula I which is capable of inhibiting fungal and/or parasitic activity.

"Recipient" includes mammals, preferably, humans.

DETAILED DESCRIPTION

It has now been found that compounds represented by structure I are useful as antifungal and antiparasitic agents or as an intermediate thereof. The most convenient means of producing compounds represented by structure I is by modifying naturally occurring compounds.

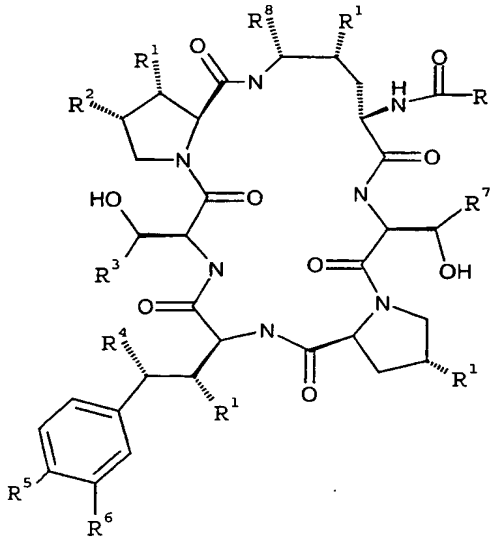
For illustrative purposes, Scheme I (below) starts with a specific echinocandin derivative. However, one can begin with any natural product, semi-synthetic or synthetic Echinocandin-type compound containing one or more hydroxy groups that are capable of being derivatized with one of the sugar moiety represented below:



or

R^9 is defined as described above.

The term "echinocandin-type compounds" refers to compounds having the following general structure including any simple derivatives thereof:



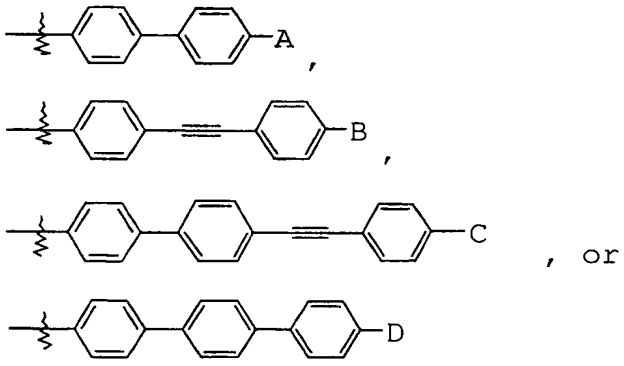
wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R^1 is independently -H or -OH; R^2 is -H or $-CH_3$; R^3 is -H, $-CH_3$, $-CH_2CONH_2$ or $-CH_2CH_2NH_2$; R^4 is -H or -OH; R^5 is -OH, $-OPO_3H_2$, $-OPO_3HCH_3$, -

OPO_2HCH_3, or $-OSO_3H$; R^6 is -H, -OH, or $-OSO_3H$; R^7 is -H or $-CH_3$; R^8 is -H or -OH; and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

"Natural product" refers to those secondary metabolites, usually of relatively complex structure, which are of more restricted distribution and more characteristic of a specific source in nature. Suitable natural product starting materials of the Echinocandin cyclopeptide family include Echinocandin B, Echinocandin C, Aculeacin Aγ, Mulundocandin, Sporiofungin A, Pneumocandin A_0, WF11899A, and Pneumocandin B_0.

The cyclic peptides used in the present invention can be produced by culturing various microorganisms. In general, the cyclic peptides can be characterized as a cyclic hexapeptide nucleus with an acylated amino group on one of the amino acids. The amino group on the naturally-occurring cyclic peptide is typically acylated with a fatty acid group forming a side chain off the nucleus. Naturally-occurring acyl groups include, but are not limited to, linoleoyl (Echinocandin B, C and D), palmitoyl (Aculeacin Aγ and WF11899A), stearoyl, 12-methylmyristoyl (Mulundocandin), 10,12-dimethylmyristoyl (Sporiofungin A and Pneumocandin A_0).

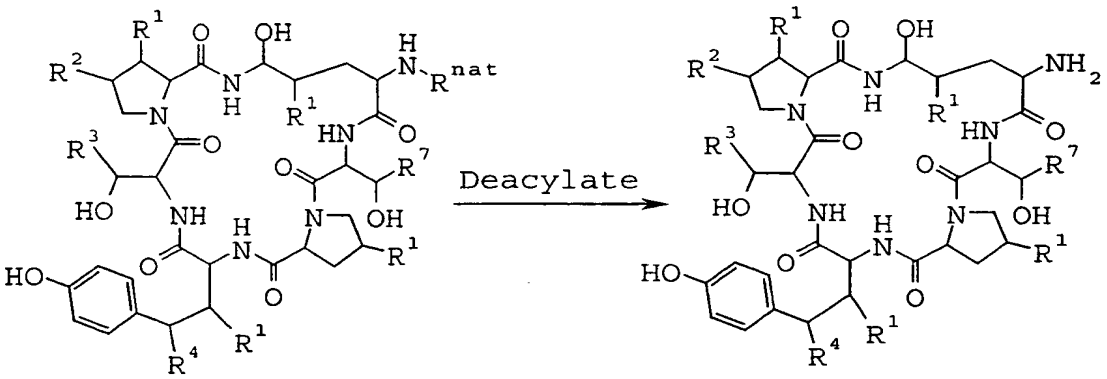
Semi-synthetic derivatives can be generally prepared by removing the fatty acid side chain from the cyclic peptide nucleus to produce a free amino group (i.e., no pendant acyl group -C(O)R). The free amine is then reacylated with a suitable acyl group. For example, the echinocandin B nucleus has been re-acylated with nonnaturally occurring side chain moieties to yield a number of antifungal agents. U.S. Patent No. 4,293,489. The N-acyl side chain includes a variety of side chain moieties known in the art. Suitable side chain moieties include substituted and unsubstituted alkyl groups, alkenyl groups, alkynyl groups, aryl groups, heteroaryl groups and combinations thereof. Preferably, the side chain contains both a linearly rigid section and a flexible alkyl section to maximize antifungal potency. Representative examples of preferred acyl side chains include R groups having the following structures:



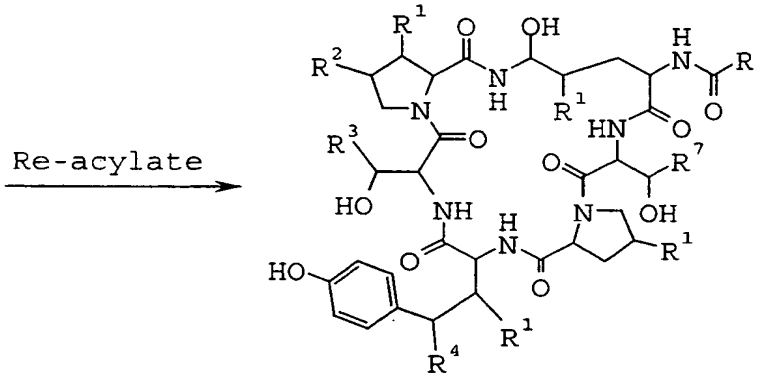
, or

where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or -O-$(CH_2)_m$-[O-$(CH_2)_n$]$_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E; m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4; X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C1-C12 alkyl, C3-C12 cycloalkyl, benzyl or C3-C12 cycloalkylmethyl.

Scheme I illustrates the general semi-synthetic route above where a natural product (Compound II(a)) is modified to provide an acylated intermediate (Compound II(c)) which is modified to provide a Compound of structure I as in Scheme II.



II(a) II(b)



II(c)

Scheme I

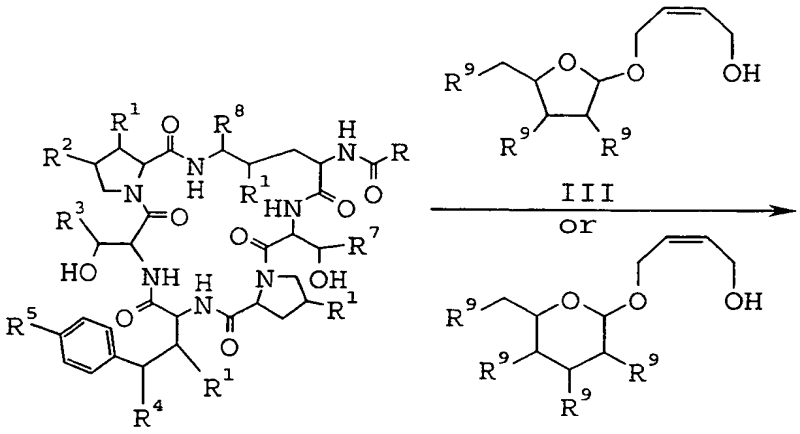
The cyclic peptides of structure II(a) can be prepared by fermentation of known microorganisms. The cyclic peptide II(a) where R^1 and R^4 are each hydroxy, R^2, R^3 and R^7 are each methyl(cyclic nucleus corresponding to A-30912A) can be prepared by the procedure in U.S. Patent No. 4,293,482. The cyclic peptide II(a) where R^1 is hydroxy, R^2, R^3 and R^7 are each methyl, and R^4 is hydrogen (cyclic nucleus corresponding to A-30912B) can be prepared by the procedure in U.S. Patent No. 4,299,763. Aculeacin can be prepared by the procedure in U.S. Patent No. 3,978,210. The cyclic peptide II(a)

where R^3 is $CH_2C(O)NH_2$, R^7 is methyl, R^2 is hydrogen, and R^1 and R^4 are hydroxy can be prepared by the procedure in U.S. Patent No. 5,198,421.

The naturally occurring cyclic peptide II(a) can be deacylated using procedures known in the art to provide an amino nucleus represented by structure II(b). This reaction is typically carried out enzymatically by exposing the naturally occurring cyclic peptide to a deacylase enzyme. The deacylase enzyme can be obtained from the microorganism *Actinoplanes utahensis* and used substantially in U.S. Patent Nos. 4,293,482 and 4,304,716. The deacylase enzyme can also be obtained from the *Pseudomonas* species. Deacylation can be accomplished using whole cells of *A. utahensis* or *Pseudomonas* or the crude or purified enzyme thereof or using an immobilized form of the enzyme. See European Patent Application No. 0 460 882. Examples of naturally occurring cyclic peptides useful as starting materials include aculeacin (palmitoyl side chain), tetrahydroechinocandin B (stearoyl side chain), Mulundocandin (branched C_{15} side chain), L-671,329 (C_{16} branched side chain), S 31794/F1 (tetradecanoyl side chain), sporiofungin (C_{15} branched side chain), FR901379 (palmitoyl side chain) and the like. A preferred naturally occurring cyclic peptide is echinocandin B (Compound II(a) where R^1, R^4 and R^8 are each hydroxy, R^2, R^3 and R^7 are each methyl, and R^{nat} is linoleoyl).

The amino nucleus II(b) can be re-acylated, as in U.S. Patent Nos. 5,646,111, and 5,693,611, to yield compounds represented by structure II(c). See Preparation 12 for an example of this transformation and U.S. Patent Nos. 5,646,111 and 5,693,611 for preparation of the acyl groups at R. Cyclic peptides II(c) where R contains 1 or more heterocyclic rings can be prepared as in U.S. Patent No. 5,693,611.

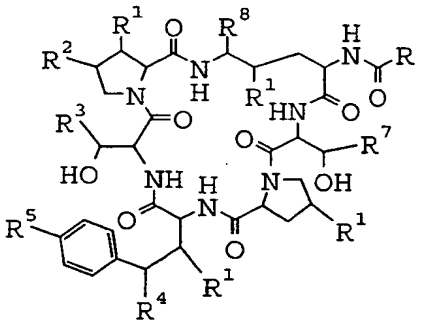
Compound I can be prepared from Compound II(c) as illustrated in Scheme 2 where R^4 and R^8 are independently hydrogen or hydroxy provided at least one of R^4 or R^8 is a hydroxy group and R, R^1, R^2, R^3, R^5, R^7 and R^9 are as defined above.



II(c)

R^4 and R^8 is -H or -OH

IV

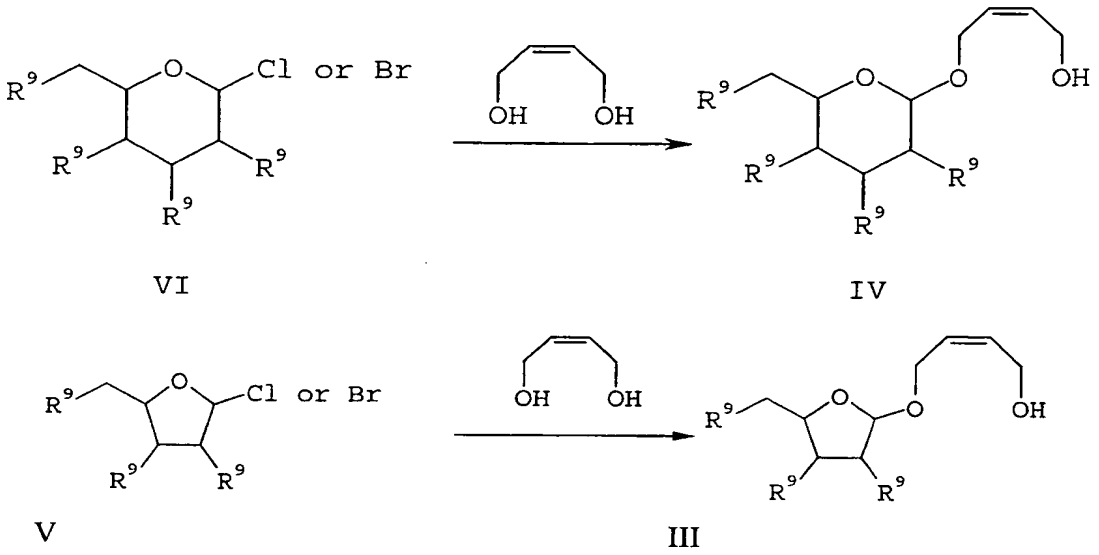


I

Scheme 2

A mixture of mono- and bis-coupled compounds represented by structure I can be prepared by adding a protected compound of III or IV to Compound II(c) dissolved or suspended in a suitable solvent in the presence of a suitable acid. A convenient and preferred solvent for the reaction is 1,4-dioxane while a convenient and preferred acid is p-toluenesulfonic acid. The reaction can be performed at from 0°C to the reflux temperature of the mixture but is typically performed at ambient temperatures for about 4 hours. See Example 1 below for further instruction on reaction conditions. Each mono and bis isomer can be separated and deprotected separately.

Compounds III and IV can be prepared from Compounds V and VI, respectively, as illustrated in Scheme 3 below where R^9 is as described above.

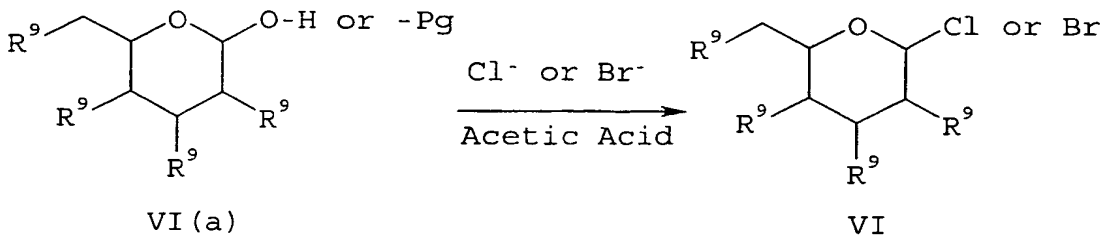


Scheme 3

2-Butene-1,4-diol can be added to a chloro or bromo sugar of formula VI, preferably one that is protected, dissolved in a suitable solvent, in the presence of a thermodynamic base, preferably silver carbonate or silver triflate, to form a compound of formula IV. Typically, the 1,4-diol can serve as the solvent and is used in a large molar excess. Furthermore, the silver carbonate is also used in a molar excess relative to the compound VI, typically on the order of about 2 equivalents. The reaction is typically performed at ambient temperature for about 18 hours. For further instruction on this conversion, see Preparation 11 below. Compound III can be prepared in an analogous manner from Compound V.

Compounds V and VI are known in the art and to the extent not commercially available can be synthesized by techniques well known in the synthetic chemical arts. See, Collins and Ferrier, "Monosaccharides: Their Chemistry and Their Roles in Natural Products," John Wiley and Sons, New York, NY, 1995, and "Methods in Carbohydrate Chemistry", Vol VI, Academic Press, New York, N.Y., 1980.

For example, Compound VI (Compound V by analogy) can be prepared as illustrated in Scheme 4 below where R^9 is as described above.

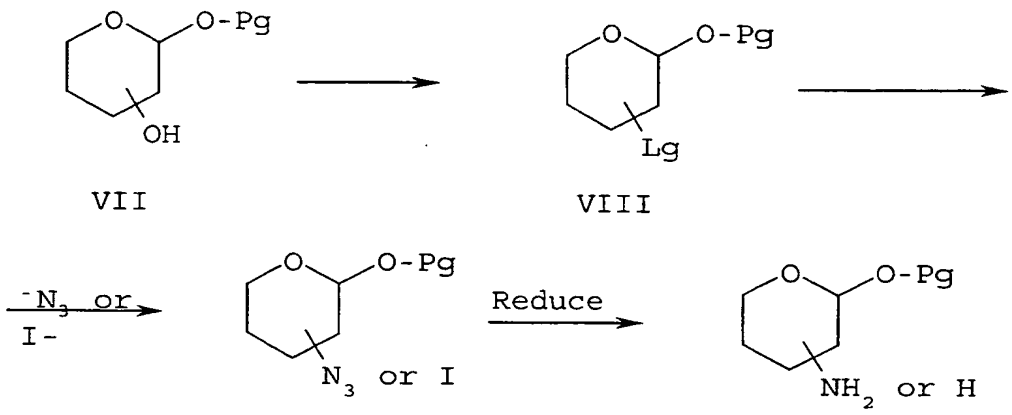


VI(a) VI

Scheme 4

Compound VI(a), dissolved or suspended in a suitable solvent, can be treated with a source of chloride or bromide ion, to provide Compound VI. Suitable sources of ion include acetyl chloride, hydrochloric acid, hydrobromic acid, mixtures thereof, and the like. A preferred solvent is the source of ion i.e. a preferred method of performing the reaction is to run it neat. See Preparations 8 and 9 below.

Compound VI(a) where R^9 is hydroxy at each occurrence are known as carbohydrates or monosaccharides (sugars). These sugars can be modified by replacing one or more hydroxy groups with hydrogen, azide, or amino to provide the rest of the compounds having structure VI(a) including disaccharides (or polysaccharide) where R^9 is a second sugar moiety (see, Examples 10 and 11). Such compounds can be prepared as illustrated in Scheme 5 below where Lg is an activated hydroxy leaving group.



VII VIII IX X

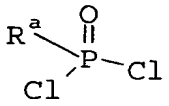
Scheme 5

A commercially available Compound VII can have its hydroxy group(s) activated for nucleophilic displacement by standard techniques known in the art. For example, the hydroxy group can be sulfonylated with methane-, benzene-, or p-toluene-sulfonyl chloride (or bromide) to provide Compound VIII where Lg is $-OSO_2Me$, $-OSO_2$-phenyl, or $-OSO_2$-*p*-toluenyl. An example of this transformation is illustrated in Preparation 1

below. At this point, the leaving group can be displaced by azide ion, *e.g.*, from sodium or potassium azide as in Preparation 2. Alternatively, the leaving group can be displaced by iodide ion from, *e.g.*, sodium or potassium iodide as in Preparation 3. The resulting Compound IX can be reduced to form Compound X where one or more of R^9 is amino or hydrogen by catalytic hydrogenation, as described in Preparation 4, or with a reducing agent such as nickel chloride hexahydrate. It is preferred that when an amino group is desired in the final product Compound I, that any azido groups are converted to amino groups after coupling to Compound II(a).

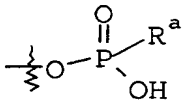
Compound I, where any of R^9 is an amino group can be formed from the a Compound I where R^9 is azido as described by analogous procedures well known in the art. See, *e.g.*, Larock, "Comprehensive Organic Transformations," pg. 409, VCH Publishers, New York, N.Y., 1989.

Compound I where R^5, R^9, R^{9a}, R^{9b}, and/or R^{9c} is a hydroxy group, can be phosphorylated or phosphonylated by reaction with an appropriately substituted dichloro-phosphate or phosphonic acid of formula V



V

in the presence of a suitable base to provide, following an aqueous work-up, to produce Compound I where R^5, R^9, R^{9a}, R^{9b}, and/or R^{9c} are moieties of the formula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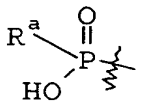

, respectively.

Suitable bases include lithium trimethylsilanolate (LiOTMS), and lithium bis(trimethylsilyl)amide (LHMDS). A convenient and preferred solvent is an aprotic solvent such as tetrahydrofuran and/or dimethylformamide. For further instruction on such a transformation, see U.S. Patent No. 5,693,611, incorporated herein by reference.

Alternatively, the compounds represented by structure I where R^{9b} is hydroxy and/or R^{9c} is hydroxymethyl can be sulfated by reaction with a suitable sulfation reagent by the procedures taught in Guiseley et al., *J. Org. Chem.*, 26:1248 (1961).

Compound I having protecting groups can have its protecting group(s) removed to form a deprotected Compound I. Initial choices of protecting groups, and methods for

their removal, are well known in the art. See, *e.g.*, *Greene*. Preferred choices and methods can be found in the Examples section which follows, *e.g.*, Example 8.

Pharmaceutical salts are typically formed by reacting Compound I with an equimolar or excess amount of acid or base. The reactants are generally combined in a mutual solvent such as diethylether, tetrahydrofuran, methanol, ethanol, isopropanol, benzene, and the like for acid addition salts, or water, an alcohol or a chlorinated solvent such as methylene chloride for base addition salts. The salts normally precipitate out of solution within about one hour to about ten days and can be isolated by filtration or other conventional methods.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, ethanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, tartaric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

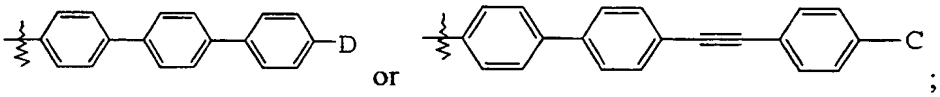
The particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

Preferred pharmaceutical acid addition salts are those formed with mineral acids such as hydrochloric acid and sulfuric acid, and those formed with organic acids such as maleic acid, tartaric acid, and methanesulfonic acid. Preferred pharmaceutical base addition salts are the potassium and sodium salt forms.

The optimal time for performing the reactions of Schemes 1 - 5 can be determined by monitoring the progress of the reaction by conventional chromatographic techniques. Choice of reaction solvent is generally not critical so long as the solvent employed is inert to the ongoing reaction and sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction. Unless otherwise indicated, all of the reactions described herein are preferably conducted under an inert atmosphere. A preferred inert atmosphere is nitrogen. Once a reaction is complete, the intermediate compound can be isolated by procedures well-known in the art, for example, the compound can be crystallized or precipitated and then collected by filtration, or the

reaction solvent can be removed by extraction, evaporation or decantation. The intermediate compound can be further purified, if desired, by common techniques such as crystallization, precipitation, or chromatography over solid supports such as silica gel, alumina and the like, before carrying out the next step of the reaction scheme.

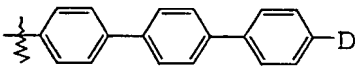
Preferred compounds of the present invention are those compounds represented by structure I wherein R^1 is hydroxy at each occurrence; R^2, R^3 and R^7 are each methyl; R is a moiety of the formula:



;

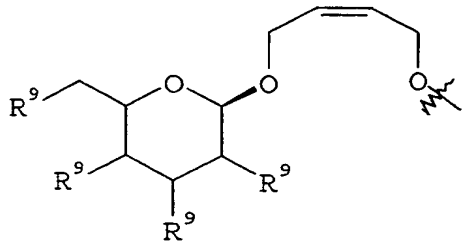
R^4 is hydroxy; and R^a is C_1-C_4 alkyl or C_1-C_4 alkoxy; or a pharmaceutically acceptable salt or solvate thereof.

More preferable are those compounds wherein R^5 is hydroxy; R is a moiety of the formula



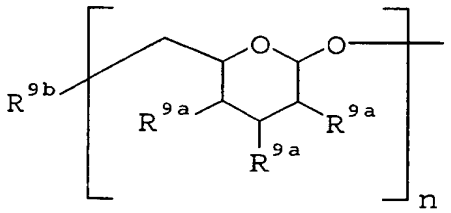
;

R^4 is a moiety of the formula



;

D is hydrogen or C3-C7 alkoxy; R^9 is independently hydrogen, hydroxy, amino, or a moiety of the formula



where R^{9b} is $-OPO_2R^a$, $-OSO_3H$, -H, $-NH_2$, -OH, -O-Pg, or -NH-Pg and n is 1, 2, or 3; or a pharmaceutically acceptable salt thereof.

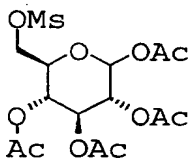
Even more preferable are those compounds wherein D is n-pentoxy; R^9 is independently -OH, $-NH_2$ or $-OPO_2R^a$; or a pharmaceutical salt or solvate thereof.

Most preferred are those compounds wherein R^9 is hydroxy at each occurrence; and R^{9b} is $-OPO_2R^a$, where R^a is methyl or methoxy; or a pharmaceutically acceptable salt or solvate thereof.

The following Preparations and Examples further describe how to synthesize the compounds of the present invention but do not limit the invention. All references cited herein are hereby incorporated by reference. The terms fast atom bombardment mass spectroscopy and high performance liquid chromatography are abbreviated "MS(FAB)" and "HPLC" respectively. The following acronyms represent the corresponding chemical moieties: Ms = methanesulfonyl; Ac = acetyl; Me = methyl; and Tos = tosyl (or p-toluenesulfonyl).

Preparation 1

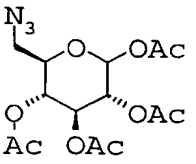
1,2,3,4-Tetra-O-Acetyl-6-Deoxy-6-Methanesulfonyl-β-D-Glucopyranose



In a 100 mL round bottom flask containing 50 mL dichloromethane at 0°C was placed 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (4.62 g, 13.26 mmol). To this solution was added triethylamine (2.77 mL, 19.90 mmol) followed by dropwise addition of methanesulfonyl chloride (1.23 mL, 15.9 mmol). The reaction was then warmed to room temperature and stirred for 3 hours at which time the reaction was diluted with 100 mL dichloromethane. The organic layer was then washed two times each with 50 mL of water, 1N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to yield 4.45 g of crude title compound as a white solid which was used directly in Preparation 2. (79%).

Preparation 2

1,2,3,4-Tetra-O-Acetyl-6-Azido-6-Deoxy-β-D-Glucopyranose

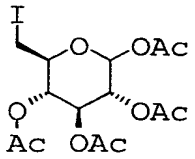


A 100 mL round bottom flask was charged with 40 mL anhydrous dimethylformamide, sodium azide (2.19 g, 33.6 mmol), and crude 1,2,3,4-tetra-O-acetyl-6-deoxy-6-methanesulfonyl-β-D-glucopyranose (1.9374 g, 4.54 mmol). The resulting

homogeneous solution was heated to 70°C and allowed to react for 10 hours. The reaction was then diluted with 200 mL of ethyl acetate and washed with copious amounts of water. The organic layer was dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The resulting brown solid was purified by column chromatography over silica gel to yield 668.3 mg of the title compound (39.5%). MS(FAB) calculated for $C_{14}H_{19}N_3O_9$ (M - $OCOCH_3$) 314.1, found 314.1.

Preparation 3

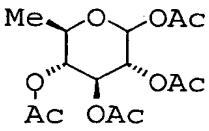
1,2,3,4-Tetra-O-Acetyl-6-Deoxy-6-Iodo-β-D-glucopyranose



A 1 L round bottom flask containing 500 mL of methyl ethyl ketone was charged with 1,2,3,4-tetra-O-acetyl-6-deoxy-6-methanesulfonyl- β-D-glucopyranose (4.45 g, 10.44 mmol) and sodium iodide (15.73 g, 104.9 mmol). The reaction was heated at reflux for 24 hours. The solvent was removed *in vacuo* and the resulting residue was taken up in 250 mL dichloromethane. The organic layer was washed with sodium thiosulfate (2 x 100 mL), water (2 x 100 mL) and once with 100 mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to yield crude 1,2,3,4-tetra-O-acetyl-6-deoxy-6-iodo-β-D-glucopyranose as a white solid (4.99 g) which was used directly in Preparation 4.

Preparation 4

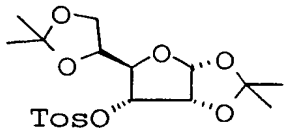
1,2,3,4-Tetra-O-Acetyl-6-Deoxy-β-D-Glucopyranose



1,2,3,4-Tetra-O-acetyl-6-deoxy-6-iodo-β-D-glucopyranose (251.6 mg, 0.549 mmol) was dissolved in 20 mL of ethanol. To this solution was added 1 mL of triethylamine and 5% palladium on carbon (50.0 mg). The reaction mixture was exposed to 60 psi of hydrogen in a Parr apparatus at room temperature for 5 hours. The palladium on carbon was filtered off and the ethanol was removed *in vacuo* to yield a white solid. Purification via column chromatography over silica gel yielded 82.3 mg of the title compound as a white solid. (45%). MS(FAB) calculated for $C_{14}H_{20}O_9$ (M+): 332.1. Found: 331.1.

Preparation 5

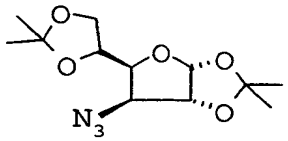
1,2,5,6-Diacetone-4-p-Toluenesulfonyl-*D*-Allofuranose



A 500 mL round bottom flask containing 160 mL of pyridine was charged with 1,2,5,6-diacetone-D-allofuranose (40.72 g, 156.44 mmol) and *p*-toluenesulfonyl chloride (45.67 g, 239.53 mmol). The reaction was allowed to stir at room temperature for 27 hours. The reaction mixture was poured into 1.5 L of ice water and, upon melting, was filtered and dried in a vacuum oven at 30°C to yield 56.74 g of the title compound which was used crude in Preparation 6.

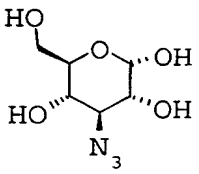
Preparation 6

1,2,5,6-Diacetone-4-p-Azido-D-Allofuranose



In a 2 L round bottom flask containing 1 L of dimethylformamide was added 1,2,5,6-diacetone-4-p-toluenesulfonyl-D-allofuranose (56.44 g, 136.17 mmol) and sodium azide (142.12 g, 2.186 mol). The reaction mixture was heated to reflux and allowed to react for 20 hours. The reaction was cooled to room temperature and the dimethylformamide was removed *in vacuo*. The resulting residue was partitioned between 250 mL ethyl acetate and 250 mL water. The organic layer was washed with 300 of water and brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed *in vauco* to obtain a crude brown oil. Purification via column chromatography over silica gel (10% ethyl acetate/hexanes) yielded the title compound.

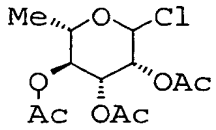
Preparation 7



1,2,5,6-Diacetone-4-p-azido-D-allofuranose was suspended in 50 mL of water in a 500 mL round bottom flask. To this suspension was added Dowex 50 X 8-100 acidic resin (20 g), the reaction mixture was heated at 60°C for 16 hours. The resin was filtered and the filtrate was lyophilized to yield 9.92 g of the title compound as a white solid.

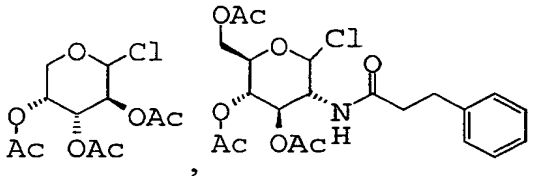
Preparation 8

α-D-Acetochlororhamnose



In a 25 mL round bottom flask containing 10 mL of acetyl chloride was placed 1.0117 g of L-rhamnose. The reaction was stirred for 48 h at room temperature. The reaction was diluted with 100 mL of dichloromethane and washed with 50 mL ice water and then 50 mL of cold saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* and the product used without further purification.

The following compounds were prepared by the procedure of Preparation 8: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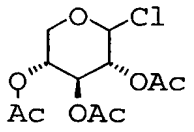
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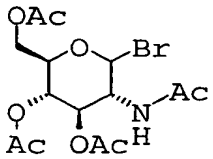
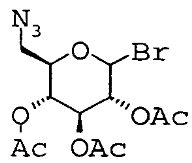
Preparation 9

2,3,4-Tri-O-Acetyl-6-Deoxy-β-D-Glucopyranosyl Bromide:



In a 10 mL round bottom flask containing 10 mL of glacial acetic acid was placed 6-deoxyglucose (332.3 mg) and the reaction was cooled to 0°C. Hydrobromic acid in glacial acetic acid (5 mL of a 30 wt. % solution) was added dropwise. The reaction was stirred for 4 hours. The reaction was diluted with 100 mL of dichloromethane and washed with 50 mL ice water and then 50 mL of cold saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield the title compound as a yellow solid (636.5 mg, 85.4%) and the product was used without further purification. MS(FAB) calculated for $C_{12}H_{17}O_7Br$ (M - Br) 273.1, found 273.1.

The following compounds were prepared by the procedure of Preparation 9:



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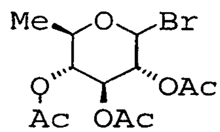

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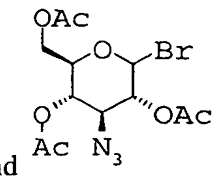

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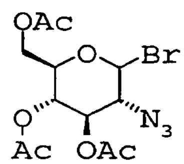
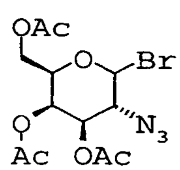
Preparation 10

3,4,6-Tri-O-Acetyl-2-Azido-2-Deoxy-β-D-Glucopyranosyl Bromide



A 1 L flask containing 400 mL of acetonitrile was charged with sodium azide (7.75 g, 119.2 mmol) and ceric ammonium nitrate (120.7 g, 219.4 mmol). The resulting suspension was cooled to -30°C and a solution of tri-O-acetyl-D-glucal (20.75 g, 76.22 mmol) in 100 mL acetonitrile was added to it dropwise. The reaction mixture was stirred at -30°C for 20 hours and then warmed to room temperature, taken up in 800 mL of diethyl ether and washed with water (3 x 250 mL). The organics were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* to yield an oil. This oil was placed in a 1 L flask containing 400 mL of acetonitrile and lithium bromide (33.53 g, 386.1 mmol) and stirred at room temperature for at least 4 hours. The solvent was removed *in vacuo* and the resulting residue was taken up in 400 mL of dichloromethane. The organic layer was washed with water (2 x 250 mL), dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield the title compound as a dark yellow oil which was used directly without further purification.

The following compounds were prepared by the procedure of Preparation 10:



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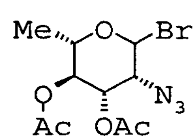

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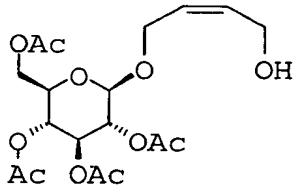
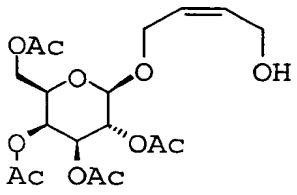
Preparation 11

4-Acetoglucosyl-2-Butenol

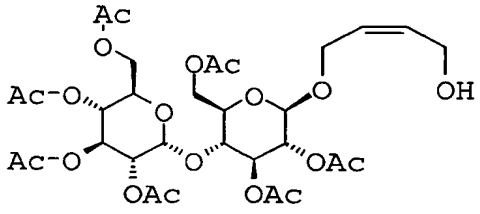


A flask was charged with acetobromoglucose (10.05 g, 24.44 mmol), silver carbonate (13.64 g, 49.47 mmol) and 200 mL of 2-butene-1,4-diol. The reaction mixture was allowed to stir for 18 hours at room temperature. The crude reaction mixture was filtered over a celite pad to remove silver salts and washed several times with ethyl acetate. The organics were then washed several times with copious amounts of water to removed unreacted 2-butene-1,4-diol. The organic layer was then dried with magnesium sulfate and concentrated in vacuo to yield a yellow oil. Silica gel column chromatography of the oil eluting with 70% ethyl acetate in hexanes yielded 2.37 g of the title compound. (23.2%).

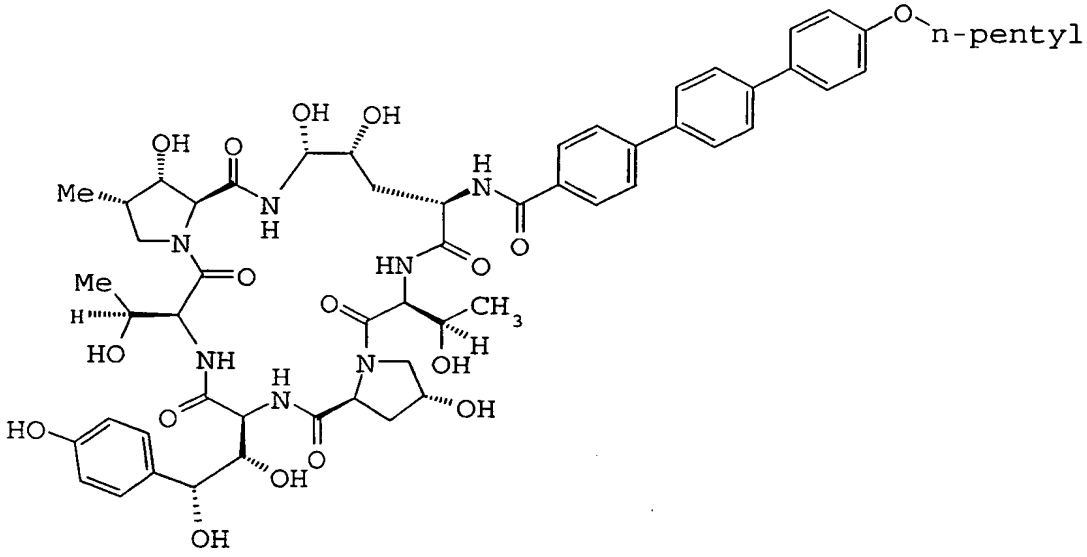
The following compounds were prepared by the procedure of Preparation 11:



and



Preparation 12

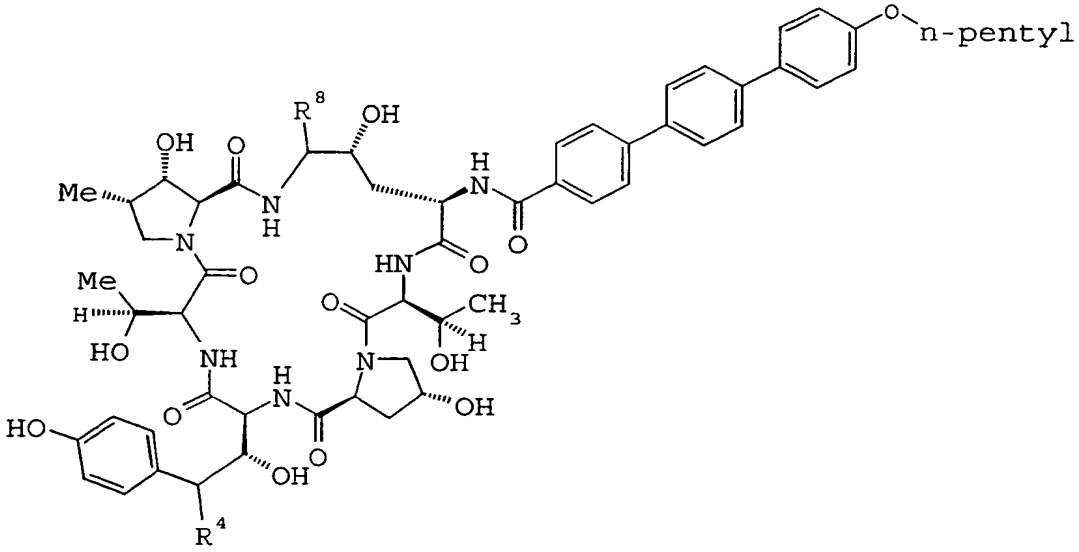


The A-30912A nucleus (60.2 mmol) and the 2,4,5-trichlorophenol ester of [[(4"-pentyloxy)-1,1':4',1"-terphenyl]-4-carboxylic acid (26.0 g, 48.2 mmol) were combined in 8.5 L of dimethylformamide. The resultant reaction mixture was stirred for approximately 48 hours at room temperature and then the solvent was removed *in vacuo* to provide a residue. This residue was slurried in ether, collected by filtration, washed with methylene chloride and then dissolved in methanol or a 1:1 (v/v) acetonitrile/water mixture. The resultant solution is subjected to reverse phase HPLC (C18; eluent of 20-40% aqueous acetonitrile containing 0.5% monobasic ammonium phosphate (w/v); 20 mL/min.; 230 nm). After removing the unreacted A30912A nucleus, the desired product is eluted from the column using an eluent of aqueous acetonitrile. The fractions containing the desired product are combined and then concentrated *in vacuo* or lyophilized to provide 18 g of the title compound. MS(FAB):

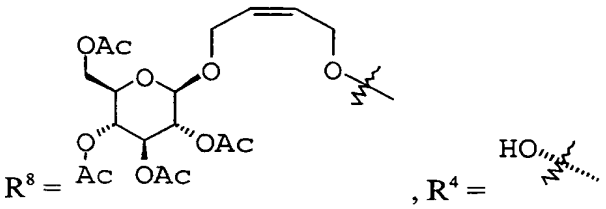
1140.5103 (M^{+1}).

Examples 1-14

Examples 1 - 14 have the following base structure:



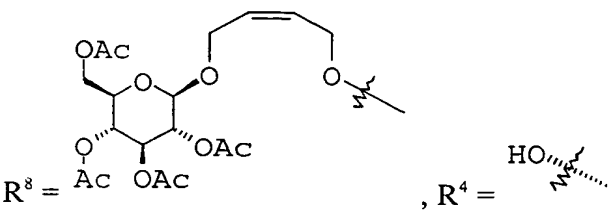
Example 1



The compound of Preparation 12 (269.8 mg, 0.237 mmol), the first compound of Preparation 11 (508.1 mg, 1.214 mmol), p-toluenesulfonic acid (100.8 mg, 0.530 mmol) and 15 mL of 1,4-dioxane were placed in a flask and stirred at room temperature for 4 hours. The crude reaction mixture was filtered and purified via HPLC eluting with 40% water in acetonitrile at 60 mL/minute using a 3 x 40 x 100 mm Novapak C_{18} column to afford 12.4 mg of the title compound. (3.4%). MS(FAB) (m/e): 1562.7 (M+Na)

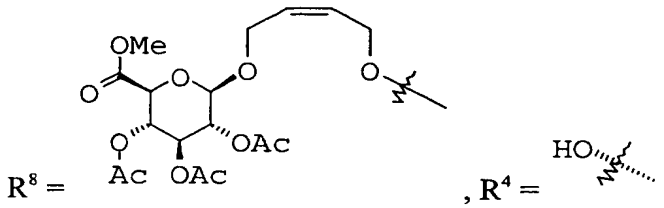
Examples 2 - 7 were prepared by the procedure of Example 1.

Example 2

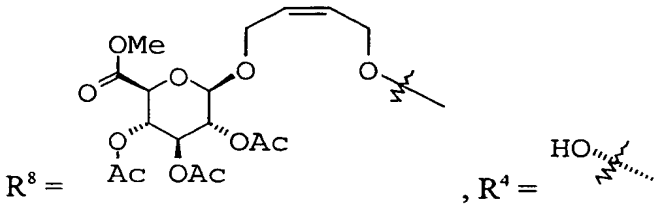


MS(FAB) (m/e): 1563.5 (M+Na)

Example 3

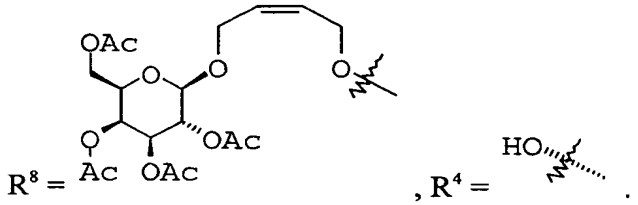


Example 4



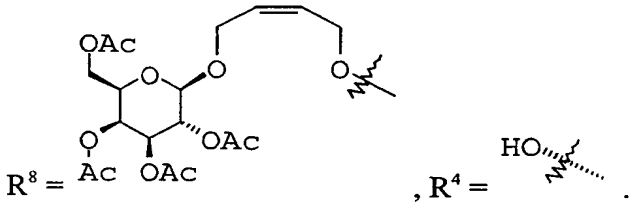
MS(FAB) (m/e): 1549.0 (M+Na)

Example 5



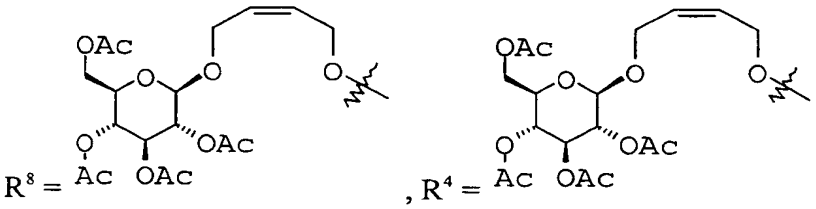
MS(FAB) (m/e): 1562.7 (M+Na)

Example 6



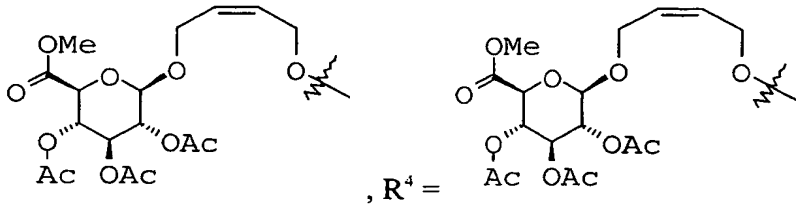
MS(FAB) (m/e): 1563.7 (M+Na)

Example 7



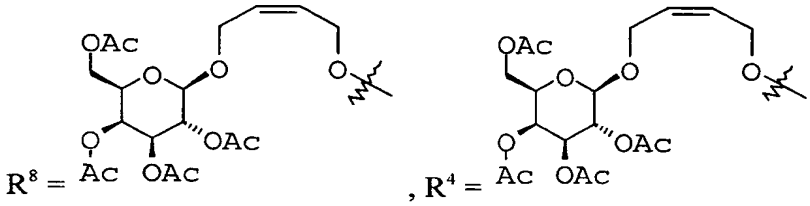
MS(FAB) (m/e): 1940.8 (M+); MS(FAB) (m/e): 1964.0 (M+Na)

Example 8



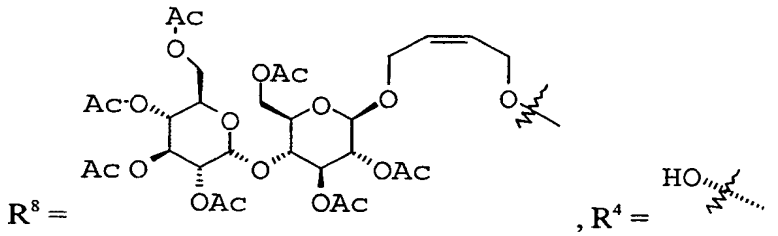
MS(FAB) (m/e): 1935.2 (M+Na); MS(FAB) (m/e): 1935.1 (M+Na)

Example 9

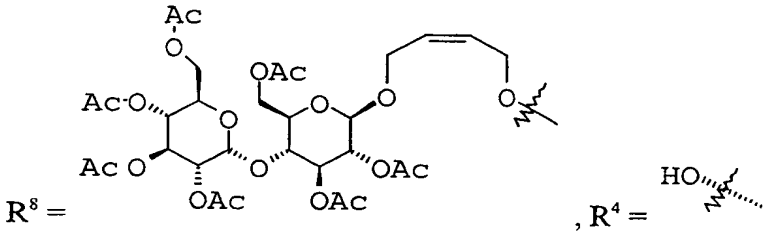


MS(FAB) (m/e): 1963.9 (M+Na); MS(FAB) (m/e): 1963.9 (M+Na)

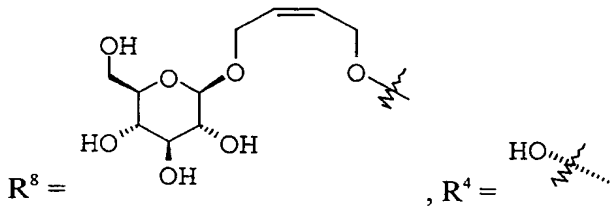
Example 10



Example 11



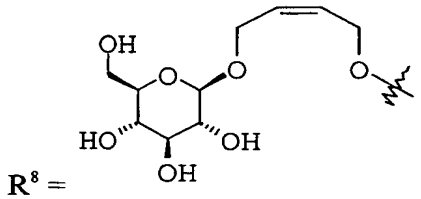
Example 12

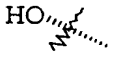


The compound of Example 1 (9.3 mg, 0.0060 mmol), potassium carbonate (5.3 mg, 0.0038 mmol), and 4 mL of a 50% mixture of methanol in water were combined and stirred for 30 minutes at room temperature. The crude reaction mixture was filtered and purified via HPLC eluting with 40% water in acetonitrile at 60 mL/minute using a 3 x 40 x 100 mm Novapak C_{18} column to afford 5.1 mg of the title compound. (62%) MS(FAB) (m/e): 1373.7 (M+).

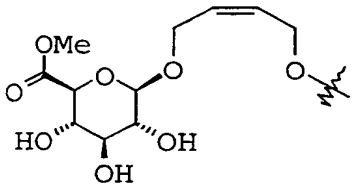
Examples 13 - 22 were prepared by the procedure of Example 1.

Example 13



R^8 = , R^4 = 

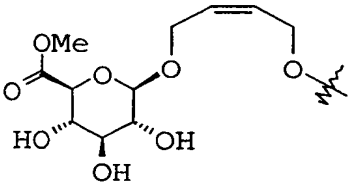
Example 14

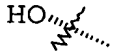


R^8 = , R^4 = 

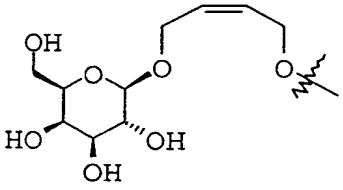
MS(FAB) (m/e): 1427.5 (M+Na)

Example 15



R^8 = , R^4 = 

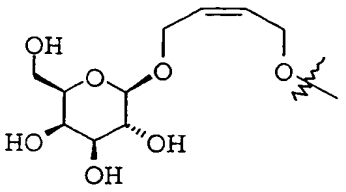
Example 16



R^8 = , R^4 = 

MS(FAB) (m/e): 1372 (M+).

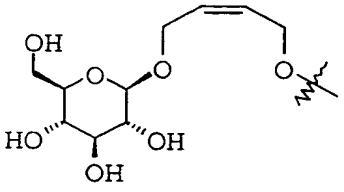
Example 17



R^8 = , R^4 = .

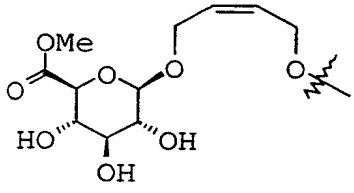
MS(FAB) (m/e): 1372 (M+).

Example 18



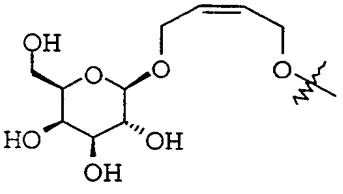
R^8 = , R^4 =

Example 19



R^8 = , R^4 =

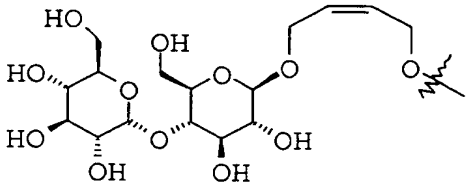
Example 20



R^8 = , R^4 =

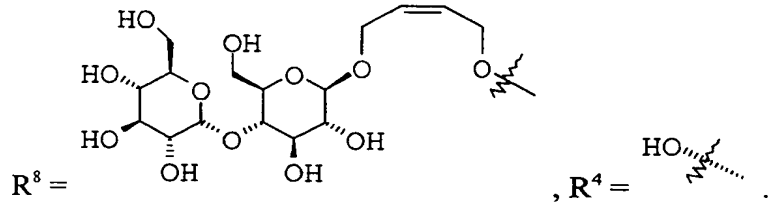
MS(FAB) (m/e): 1605.8 (M+).

Example 21



R^8 = , R^4 =

Example 22



Representative examples of Compound I exhibit antifungal and antiparasitic activity. For example, Compound I inhibits growth of various infectious fungi including *Candida spp.* such as *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, or *C. tropicalis*, *C. lusitaniae*; *Torulopus spp.* such as *T. glabrata*; *Aspergillus spp.* such as *A. fumigatus*; *Histoplasma spp.* such as *H. capsulatum*; *Cryptococcus spp.* such as *C. neoformans*; *Blastomyces spp.* such as *B. dermatitidis*; *Fusarium spp.*, *Trichophyton spp.*, *Pseudallescheria boydii*, *Coccidioides immitis*, *Sporothrix schenckii* and the like.

Antifungal activity of a test compound is determined *in vitro* by obtaining the minimum inhibitory concentration (MIC) of the compound using a standard agar dilution test or a disc-diffusion test. The compound is then tested *in vivo* (in mice) to determine the effective dose of the test compound for controlling a systemic fungal infection.

Accordingly, representative compounds of the present invention were tested for, and displayed, antifungal activity against at least one of the following fungii: *C. albicans*, *C. parapsilosis*, *C. neoformans*, *Histoplasma spp*, and *A. fumigatus*.

The compounds of the invention also inhibit the growth of certain organisms primarily responsible for opportunistic infections in immunosuppressed individuals. For example, the compounds of the invention inhibit the growth of *Pneumocystis carinii* the causative organism of pneumocystis pneumonia (PCP) in AIDS and other immunocompromised recipients. "Topley and Wilson's Microbiology and Microbial Infections," Vol. 5, Ch. 22, Oxford University Press, Inc., New York, N.Y., 1998. Other protozoans that are inhibited by compounds of formula I include *Plasmodium spp.*, *Leishmania spp.*, *Trypanosoma spp.*, *Cryptosporidium spp.*, *Isospora spp.*, *Cyclospora spp.*, *Trichomonas spp.*, *Microsporidiosis spp.* and the like.

The dose of Compound I administered varies depending on such factors as the nature and severity of the infection, the age and general health of the recipient and the tolerance of the recipient to the active ingredient. The particular dose regimen likewise can vary according to such factors and can be given in a single daily dose or in multiple doses during the day. The regimen can last from about 2 - 3 days to about 2 - 3 weeks or longer. A typical daily dose (administered in single or divided doses) contains a dosage

level of from about 0.01 mg/kg to about 100 mg/kg of body weight of the active compound of this invention. Preferred daily doses are generally from about 0.1 mg/kg to about 60 mg/kg, more preferably from about 2.5 mg/kg to about 40 mg/kg.

Compound I can be administered parenterally, for example using intramuscular, sub-cutaneous, or intra-peritoneal injection, nasal, or oral means. In addition to these methods of administration, Compound I can be applied topically for skin infections.

The present invention also provides pharmaceutical formulations useful for administering the compounds of the invention. The active ingredient in such formulations comprises from 0.1% to 99.9% by weight of the formulation, more generally from about 10% to about 30% by weight.

For parenteral administration, the formulation comprises Compound I and a physiologically acceptable diluent such as deionized water, physiological saline, 5% dextrose and other commonly used diluents. The formulation can contain a solubilizing agent such as a polyethylene glycol or polypropylene glycol or other known solubilizing agent. Such formulations can be made up in sterile vials containing the active ingredient and one or more excipients in a dry powder or lyophilized powder form. Prior to use, a physiologically acceptable diluent is added and the solution withdrawn via syringe for administration to the recipient.

The present pharmaceutical formulations are prepared by known procedures using known and readily available ingredients. In making the compositions of the invention, the active ingredient will generally be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it can be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active ingredient, soft and hard gelatin capsules, suppositories, sterile injectable solutions, sterile packaged powders and the like.

For oral administration, the active ingredient is filled into gelatin capsules or formed into tablets. Such tablets can also contain a binding agent, a dispersant or other suitable excipients suitable for preparing a proper size tablet for the dosage and particular Compound represented by structure I. For pediatric or geriatric use the active ingredient can be formulated into a flavored liquid suspension, solution or emulsion. A preferred oral formulation is linoleic acid, cremophor RH-60 and water and preferably in the

amount (by volume) of 8% linoleic acid, 5% cremophor RH-60, 87% sterile water and Compound I in an amount of from about 2.5 to about 40 mg/mL.

For topical use the active ingredient can be formulated with a dry powder for application to the skin surface or it can be formulated in a liquid formulation comprising a solubilizing aqueous liquid or non-aqueous liquid, *e.g.*, an alcohol or glycol.

Formulations

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. The term "active ingredient" refers to a compound of structure I or a pharmaceutically acceptable salt or solvate thereof.

Formulation Example 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation Example 2

A tablet is prepared using the ingredients below.

	Quantity (mg/capsule)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation Example 3

An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required

amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation Example 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl-pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation Example 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat

necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of active ingredient per 5 mL dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to total	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

An intravenous formulation can be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 mL

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 mL per minute.